IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER INTELLECTUAL PROPERTY GMBH, ET AL.,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 1:17-cv-00812-RGA
INVAGEN PHARMACEUTICALS, INC.,	)	
Defendant.	)	

DEFENDANT INVAGEN PHARMACEUTICALS, INC.'S ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS

Defendant InvaGen Pharmaceuticals, Inc., by and through its undersigned counsel, and for its Answer responds to the separately-numbered paragraphs of Plaintiffs Bayer Intellectual Property GmbH, Bayer AG and Janssen Pharmaceuticals, Inc.'s Complaint, as follows:

1. Defendant admits that Plaintiffs' Complaint purports to assert claims of infringement of U.S. Patent No. 9,539,218 ("the '218 patent") under the Patent Laws of the United States and, in particular, 35 U.S.C. § 271(e)(2); however, Defendant denies that there is any factual or legal basis for any of Plaintiffs' claims against it in this action, and therefore, Defendant denies the allegations in this Paragraph.

2. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 2 of Plaintiffs' Complaint, and therefore, denies the same.

3. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 3 of Plaintiffs' Complaint, and therefore, denies the same.

4. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 4 of Plaintiffs' Complaint, and therefore, denies the same.

5. Admitted.

6. Defendant admits that it is engaged in the development of unique generic and branded drug products and does so in compliance with the Federal Food, Drug, and Cosmetic Act. Except as so admitted, Defendant denies the allegations of Paragraph 6 of Plaintiffs' Complaint.

7. Admitted.

8. Defendant admits that it is engaged in the development of unique generic and branded drug products and does so in compliance with the Federal Food, Drug, and Cosmetic Act. Except as so admitted, Defendant denies the allegations of Paragraph 8 of Plaintiffs' Complaint.

9. Defendant admits that it is engaged in the development of unique generic and branded drug products and does so in compliance with the Federal Food, Drug, and Cosmetic Act. Except as so admitted, Defendant denies the allegations of Paragraph 9 of Plaintiffs' Complaint.

10. Defendant incorporates each of the preceding paragraphs in their entirety as if each is fully set forth herein.

11. Paragraph 11 of Plaintiffs' Complaint states legal conclusions to which no response is required. To the extent any response is required, Defendant admits that the Complaint purports to assert claims of patent infringement under the Patent Laws of the United

States, over which this Court has subject matter jurisdiction. Except as so admitted, Defendant denies the allegations of Paragraph 11 of Plaintiffs' Complaint.

12. Paragraph 12 of Plaintiffs' Complaint states legal conclusions to which no response is required. To the extent any response is required, Defendant admits that the Complaint purports to assert claims of patent infringement under the Patent Laws of the United States, over which this Court has subject matter jurisdiction. Except as so admitted, Defendant denies the allegations of Paragraph 12 of Plaintiffs' Complaint.

13. Defendant admits that it has consented to jurisdiction in this judicial district in Case No. 1:15-cv-00902-RGA for the purposes of that litigation; that the claims of patent infringement asserted in Case No. 1:15-cv-00902-RGA arise from the filing of ANDA No. 208543 and that Defendant asserted counterclaims in Case No. 1:15-cv-00902-RGA. Defendant further admits that it consents to jurisdiction in this judicial district only for the purposes of this litigation. Except as so admitted, Defendant denies the allegations of Paragraph 13 of Plaintiffs' Complaint.

14. Defendant admits that the information set forth in Paragraph 14 appears in publicly available FDA documents. Except as so admitted, Defendant denies the allegations of Paragraph 14 of Plaintiffs' Complaint.

15. Defendant admits that the information set forth in Paragraph 15 appears in publicly available FDA documents. Except as so admitted, Defendant denies the allegations of Paragraph 15 of Plaintiffs' Complaint.

16. Defendant admits that, based on the face of Exhibit A of the Complaint, the '218 patent issued on January 10, 2017 and is entitled "Prevention and Treatment of Thromboembolic

Disorders." Except as so admitted, Defendant denies the allegations of Paragraph 16 of Plaintiffs' Complaint.

17. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 17 of Plaintiffs' Complaint, and therefore, denies the same.

18. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 18 of Plaintiffs' Complaint, and therefore, denies the same.

19. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 19 of Plaintiffs' Complaint, and therefore, denies the same.

20. Defendant is without knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 20 of Plaintiffs' Complaint, and therefore, denies the same.

21. Defendant admits that the '218 patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (a/k/a the "Orange Book") in connection with XARELTO. Except as so admitted, Defendant denies the allegations of Paragraph 21 of Plaintiffs' Complaint.

22. Defendant admits that it served a Notice Letter on May 9, 2017 in accordance with 21 U.S.C. § 355(j)(2)(B) and that said Notice Letter speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 22 of Plaintiffs' Complaint.

23. Defendant admits that the May 9, 2017 Notice Letter speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 23 of Plaintiffs' Complaint.

24. Defendant admits that the May 9, 2017 Notice Letter speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 24 of Plaintiffs' Complaint.

25. Defendant admits that the content of ANDA No. 208543 speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 25 of Plaintiffs' Complaint.

26. Denied.

27. Defendant admits that the May 9, 2017 Notice Letter speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 27 of Plaintiffs' Complaint.

28. Defendant admits that the content of ANDA No. 208543 speaks for itself. Except as so admitted, Defendant denies the allegations of Paragraph 28 of Plaintiffs' Complaint.

29. Denied.

30. Defendant admits that it has knowledge of the claims of the '218 patent. Except as so admitted, Defendant denies the allegations of Paragraph 30 of Plaintiffs' Complaint.

31. Denied.

32. Denied.

33. Denied.

34. Paragraph 34 of Plaintiffs' Complaint states legal conclusions to which no response is required. To the extent a response is required, Defendant denies the allegations in this Paragraph.

35. Admitted.

36. Defendant incorporates each of the preceding paragraphs in their entirety as if each is fully set forth herein.

37. Denied.

38. Denied.

39. Denied.

40. Denied.

41. Denied.

42. Any allegation in Plaintiffs' Complaint not expressly admitted by Defendant is hereby denied. Having answered Plaintiffs' Complaint, Defendant denies that Plaintiffs are entitled to the relief requested in Plaintiffs' Prayer for Relief or to any relief whatsoever, and Defendant requests that all such relief be denied *in toto*.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in their Answer and without admitting any allegations of the Complaint not otherwise admitted, Defendant avers and asserts the following Affirmative Defenses to Plaintiffs' Complaint:

43. Plaintiffs' Complaint fails to state any claim upon which relief may be granted.

44. The manufacture, use, or sale, offer for sale, or importation of the product that is the subject of Defendant's ANDA No. 208543 has not infringed, does not infringe, and would not, if marketed, manufactured, used, sold, offered for sale, or imported, infringe any valid or enforceable claim of the '218 patent.

45. The '218 patent has been, and is, invalid and void on the grounds that the purported invention attempted to be patented therein fails to meet one or more of the conditions of patentability specified in Title 35, United States Code, including without limitation one or more of §§ 101, 102, 103, and/or 112 of said Title, or other judicially-created bases for invalidation, such as double patenting.

46. The ’218 patent has been, and is, unenforceable and void on the grounds of inequitable conduct as more specifically detailed below in the counterclaim of inequitable conduct, the paragraphs of which are incorporated herein by reference.

47. All possible affirmative defenses may not have been alleged herein insofar as sufficient facts were not available after reasonable inquiry upon the filing of Defendant’s Answer and, therefore, Defendant reserves the right to amend its Answer to allege additional affirmative defenses if subsequent investigation and/or discovery warrants.

COUNTERCLAIMS

For its counterclaims against Plaintiffs/Counterclaim Defendants Bayer Intellectual Property GmbH, Bayer Pharma AG and Janssen Pharmaceuticals, Inc. (collectively “Counterclaim Defendants”), Defendant/Counterclaim Plaintiff InvaGen Pharmaceuticals, Inc. (“InvaGen”) states as follows:

48. InvaGen is a limited liability company duly organized and existing under the laws of the State of New York, having its principal place of business at 7 Oser Avenue, Hauppauge, New York 11788.

49. Upon information and belief, Bayer Intellectual Property GmbH is a German corporation having its principal place of business at Alfred-Nobel-Strasse 10, 40789 Mannheim am Rhein, Germany.

50. Upon information and belief, Bayer Pharma AG is a German corporation having a principal place of business at Müllerstrasse 178, 13353 Berlin, Germany.

51. Upon information and belief, Janssen Pharmaceuticals, Inc. is a Pennsylvania corporation having a principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey.

52. The Court has personal jurisdiction over Counterclaim Defendants because Counterclaim Defendants have availed themselves of the rights and privileges of this forum by suing InvaGen in this Judicial District and, upon information and belief, because of Counterclaim Defendants' systematic and continuous contacts with this District by virtue of Counterclaim Defendants' distribution of drugs for sale and use in this judicial district.

53. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the United States Code, as they involve claims arising out of the United States Patent Act, 35 U.S.C. § 1, *et seq*.

54. Venue for these Counterclaims is proper in this District in which Counterclaim Defendants' Complaint is pending.

55. As a consequence of Counterclaim Defendants' Complaint, there is an existing, continuing, actual controversy between Counterclaim Defendants on the one hand and InvaGen on the other. Counterclaim Defendants brought such action against InvaGen based on its submission of ANDA No. 208543.

56. This Court may declare the rights and legal relations for the parties pursuant to 28 U.S.C. §§ 2201 and 2202 and 35 U.S.C. § 271(e)(5), because these Counterclaims present an actual controversy within the Court's jurisdiction.

57. The Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq*., as amended by the Hatch-Waxman Amendments, sets forth the rules that the FDA follows when considering whether to approve both brand-name and generic drugs.

58. Under the Hatch-Waxman Amendments, an applicant seeking to market a new brand-name drug must prepare a New Drug Application ("NDA") for consideration by FDA. *See* 21 U.S.C. § 355. An NDA must include, among other things, the number of any patent that

claims the "drug" or a "method of using [the] drug" for which the NDA was submitted and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. *See* 21 U.S.C. §§ 355(b)(1) and (c)(2); 21 C.F.R. §§ 314.53(b) and (c)(2).

59. Upon approval of the NDA, the FDA publishes patent information for the approved drug in "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." *See* 21 U.S.C. § 355(j)(7)(A)(iii).

60. Generic drugs are versions of brand-name prescription drugs that typically contain the same active ingredients, but not necessarily the same inactive ingredients as the brand-name original.

61. Before 1984, a company that wished to make a generic version of an FDA approved drug had to file an application containing new studies showing the already-approved drug's safety and effectiveness. Preparing such an application was as time-consuming and costly as the original NDA.

62. In 1984, however, Congress enacted the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Amendments. *See* Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156 and 271(e)). Congress passed the Hatch-Waxman Amendments, which simplified the procedure for obtaining approval of generic drugs, for the purpose of decreasing the cost of pharmaceuticals through increased competition. Under the Hatch-Waxman Amendments, a generic manufacturer submits what is called an Abbreviated New Drug Application ("ANDA").

63. To receive approval of its ANDA, an applicant must show that its generic drug is "bioequivalent" to the listed reference drug. *See* 21 U.S.C. § 355(j)(4)(F). When filing an ANDA seeking approval of a generic version of a drug listed in the Orange Book, the ANDA

applicant must also "certify" that any patent information listed in the Orange Book does not preclude FDA approval of the ANDA applicant's generic version of the drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12).

64. A so-called "paragraph IV" certification asserts that the listed patent is invalid, unenforceable, and/or will not be infringed and, on that basis, seeks FDA approval of the generic product prior to patent expiration. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

65. An applicant submitting an ANDA containing a paragraph IV certification must notify both the patent holder and NDA holder of its paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(B)(i).

66. Upon receiving notice of the paragraph IV certification, the patent holder has 45 days in which to file an infringement suit against the generic manufacturer. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 35 U.S.C. § 271(e)(2)(A).

67. Patent holders have a significant strategic incentive to file suit because doing so, regardless of merit, prevents the FDA from approving the generic maker's ANDA for a period of 30 months. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

68. If the court hearing the infringement action decides the patent is valid, enforceable, and would be infringed by the product proposed in the ANDA, the FDA will not approve the ANDA until the patent expires. *See* 21 U.S.C. § 355(j)(5)(B)(iii). If, however, the court hearing the infringement action rules before the expiration of the 30-month period that the patent is invalid, unenforceable, and/or not infringed, the FDA may approve the ANDA. *Id*.

69. On or about January 10, 2017, the USPTO issued the '218 patent, entitled "Prevention and Treatment of Thromboembolic Disorders." Based on the allegations asserted in the Counterclaim Defendant's complaint Bayer Intellectual Property GmbH is the assignee of the

‘218 Patent; Bayer AG is an exclusive licensee of the ’218 patent and Janssen is an exclusive sublicensee of the ’218 patent.

70. Upon information and belief, Janssen Pharmaceuticals, Inc. is indicated in the records of the FDA as the holder of New Drug Application No. 022406 for XARELTO rivaroxaban 10 mg, 15 mg and 20 mg tablets, which are sold by Counterclaim Defendants.

71. The ‘218 patent is listed in the electronic version of the Orange Book in association with XARELTO.

72. InvaGen filed an ANDA (No. 208543) with the FDA seeking approval of its generic rivaroxaban 10 mg, 15 mg and 20 mg tablets, prior to the expiration of the ‘218 patent.

73. Because InvaGen seeks FDA approval of its generic rivaroxaban 10 mg, 15 mg and 20 mg tablets before expiration of the ‘218 patent that Counterclaim Defendants listed in the Orange Book, InvaGen’s ANDA includes paragraph IV certifications to this patent.

74. In accordance with 21 U.S.C. § 355(j)(2)(B), InvaGen notified Counterclaim Defendants in writing by the Notice Letter that it had filed ANDA No. 208543 with a certification provided for in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the ‘218 patent is invalid and thus will not be infringed by the product that is the subject of ANDA No. 208543.

75. In accordance with 21 U.S.C. § 355(j)(2)(B)(iv)(ii), the Notice Letter included a detailed statement of the factual and legal basis for the certification that the ’218 patent will not be infringed by the product that is the subject of ANDA No. 208543, is invalid and is unenforceable.

76. On June 23, 2017, Counterclaim Defendants sued InvaGen alleging infringement of the ‘218 patent.

77. By bringing suit against InvaGen, Counterclaim Defendants have taken active

steps to block InvaGen's attempt to launch its generic rivaroxaban 10 mg, 15 mg and 20 mg tablets.

78. The '218 patent will not be infringed by the manufacture, use, sale, offer for sale, or importation of InvaGen's proposed generic rivaroxaban 10 mg, 15 mg and 20 mg tablets.

79. The '218 patent is invalid and thus will not be infringed by the manufacture, use, sale, offer for sale, or importation of InvaGen's proposed generic rivaroxaban 10 mg, 15 mg and 20 mg tablets.

80. The '281 patent is unenforceable due to inequitable conduct and thus will not be infringed by the manufacture, use, sale, offer for sale, or importation of InvaGen's proposed generic rivaroxaban 10 mg, 15 mg and 20 mg tablets.

81. Because of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between InvaGen and Counterclaim Defendants as to liability for infringement of the '218 patent, which is of sufficient immediacy and reality to warrant the issuance of a Declaratory Judgment.

COUNT I
DECLARATORY JUDGMENT OF
NON-INFRINGEMENT OF THE '218 PATENT

82. InvaGen hereby realleges as if fully set forth each of the foregoing paragraphs.

83. Counterclaim Defendants have brought claims against InvaGen alleging infringement of the '218 patent.

84. There is an actual, substantial, and continuing justiciable case or controversy between InvaGen and Counterclaim Defendants having adverse legal interests of sufficient immediacy and reality to warrant the issuance of declaratory judgment concerning the non-infringement of the '218 patent.

85. The manufacture, use, sale, offer for sale, or importation of the products that are the subject of InvaGen's ANDA (No. 208543) has not infringed, does not infringe, and would not if manufactured, used, sold, offered for sale, or imported, infringe any valid or enforceable claim of the '218 patent.

86. InvaGen is entitled to a judicial declaration that the manufacture, use, sale, offer for sale, or importation of the products that are the subject of InvaGen's ANDA (No. 208543) has not infringed, does not infringe, and would not, if manufactured, used, sold, offered for sale, or imported, infringe any valid or enforceable claim of the '218 patent.

COUNT II
DECLARATORY JUDGMENT OF
INVALIDITY OF THE '218 PATENT

87. InvaGen hereby realleges as if fully set forth herein each of the foregoing paragraphs.

88. Counterclaim Defendants have brought claims against InvaGen alleging infringement of the '218 patent.

89. This counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq*. and the Declaratory Judgement Act, 28 U.S.C. §§ 2201 and 2202, and seeks a declaration that claims of the '218 patent are invalid for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, and/or 112, or other judicially-created bases for invalidity and unenforceability, such as double patenting.

90. One or more claims of the '218 patent are invalid for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, and/or 112, or other judicially-created bases for invalidation and

unenforceability, such as double patenting.

91. A present, genuine, and justiciable controversy exists between InvaGen and Counterclaim Defendants regarding, *inter alia*, the validity of the claims of the '218 patent.

92. InvaGen is entitled to a declaration that the claims of the '218 patent are invalid for failure to comply with the statutory prerequisites of Title 35 United States Code, including without limitation, one or more of §§ 101, 102, 103, and/or 112, or other judicially-created bases for invalidation and unenforceability, such as double patenting.

COUNT III
DECLARATORY JUDGMENT OF
UNENFORCEABILITY OF THE '218 PATENT

93. InvaGen hereby realleges as if fully set forth each of the foregoing paragraphs.

94. The claims of the '218 patent are unenforceable due to inequitable conduct based on material omissions made with specific intent to deceive the United States Patent and Trademark Office ("PTO").

Background

95. The '218 patent issued on January 10, 2017 on U.S. Patent Application No. 11/883,218 ("the '218 application") which was the 371 National Stage Entry of PCT/EP2006/000431 which was filed on January 19, 2006 and received a § 371 (c) date of July 16, 2008. The '218 application claims foreign priority to European Patent No. EP 05001893, which was filed on January 31, 2005.

96. Frank Misselwitz, Dagmar Kubitza ("Inventor Kubitza"), Son-Mi Park and Klaus Wehling are the named inventors of the '218 patent (collectively "Named Inventors").

97. The '218 patent is entitled "Prevention and Treatment of Thromboembolic Disorder."

98. Counterclaim Defendants content that the ’218 patent includes claims covering methods of treating thromboembolic disorders with once daily dosing with rapid release rivaroxaban tablets.

99. The Primary Examiner for the ’218 patent was Sreeni Padmanabhan. *See* the ’218 patent.

100. William F. Gray (“Gray”) is identified as the attorney of record on the documents associated with the July 27, 2007 initial filing of the ’218 application. *See* Exhibit 1, 07/27/2007 Transmittal Letter at 3 and 07/27/2007 Information Disclosure Statement at 1.

101. On information and belief, Gray was employed by Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, Connecticut at the time of the filing of the ’218 application. *Id.* 07/27/2007 Information Disclosure Statement at 1.

102. Christine M. Hansen (“Hansen”) is identified as the prosecution attorney for the ’218 application, and was involved in communicating with the PTO regarding the ’218 patent.

103. On information and belief Hansen was an attorney at Connoly Bove Lodege & Hutz LLP during the prosecution of the ’218 application. *Id.* 07/16/2008 Response to Notification of Missing Requirements at 1.

104. On information and belief Hansen’s work address during the prosecution of the ’218 application was 1007 North Orange Street, P.O. Box 2207, Wilmington, Delaware. *Id.*

105. Pre-AIA 35 U.S.C. § 103 was effective during the prosecution of the ’218 patent and states:

> (a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter

> pertains. Patentability shall not be negatived by the manner in which the invention was made.

106. Obviousness-type double patenting is a judicially created doctrine that is designed to prohibit a party from extending the duration of the right to exclude with claims in a later patent that are not patentably distinct from claims in an earlier patent. *See*, *Eli Lilly & Co. v. Barr Labs., Inc*., 251 F.3d 955, 967 (Fed. Cir. 2001).

107. On information and belief, Hansen and Gray were aware of their duty of candor and good faith in dealing with the PTO imposed by upon them by 37 C.F.R. § 1.56, including the requirement to disclose to the PTO information known to be material to patentability of the claims of the ’218 application.

108. Inventor Kubitza acknowledged his duty of candor and good faith in dealing with the PTO under C.F.R. § 1.56 in the Declaration which was submitted to the PTO on July 16, 2008, including his duty to disclose to the PTO “information which is material to the patentability of [the ’218] application.” *Id.* 07/16/2008 Combined Declaration and Power of Attorney at 3.

109. On information and belief Gray, Hansen and Kubitza, in breach of their duty of candor and good faith required by 37 C.R.R. § 1.56 and with specific intent to deceive the Examiner and/or the Board of Patent Appeals made material omissions and misrepresentations to the PTO regarding the ’218 patent.

Prosecution of the ’218 Patent and the Material Omissions

110. The ’218 application contained the following 8 claims when it was filed:

> 1. A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a

patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. The method of claim 1, wherein one dosage form is administered.

3. The use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of hours or less when orally administered to a human patient.

4. The method or use as claimed in any of Claims 1 to 3, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. The method or use as claimed in any of Claims 1 to 4, wherein the oral dosage form is a rapid-release tablet.

6. The method or use as claimed in any of Claims 1 to 5, wherein the direct factor Xa inhibitor is 5-Chloro-N-({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide.

7. A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-l ,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-l ,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

Id. 07/27/2007 Application at 15.

111. An Information Disclosure Statement ("IDS") was submitted by Gray on July 27,

2007 that disclosed the following two scientific abstracts authored by Inventor Kubitza:

> Kubitza et al. Multiple Dose Escalation Study Investigating the Pharmacodynamics, Safety, and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects, Blood, Vol. 102:11, 16 Nov. 2003, pg. 811a

> Kubitza et al., ABSTRACT 3010, Single Dose Escalation Study Investigating the Pharmacodynamics, Safety, and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy male Subjects, Blood, Vol. 102:11, 16 Nov. 2003, pg. 813a, Abstract 3010.

Id., 07/27/2007 IDS at 2. The Examiner referred to these abstracts as Kubitza et al.[1] and Kubitza et al.[2], respectively, during the prosecution of the '218 application. *Id.* 03/17/2011 Office Action at 5-6. This convention will be adopted throughout the remainder of this counterclaim.

112. On information and belief, Inventor Kubitza presented the data summarized in the Kubitza et al.[1] and Kubitza et al.[2] at scientific conferences more than one year prior to the January 31, 2005 foreign priority date claimed by the '218 patent ("Kubitza Presentations") and this information was not included in the July 27, 2007 Information Disclosure Statement in violation of Inventor Kubitza's and Gray's duties under 37 C.F.R. § 1.56.

113. On information and belief, the data disclosed during the Kubitza Presentations subsequently was published in the journal of Clinical Pharmacology & Therapeutics. *See* Exhibit 2, Kubitza et al., *Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor*, Clinical Pharmacology & Therapeutics, 78(4):412-21 (2005) (Kubitza III).

114. On information and belief, the Kubitza Presentations disclosed information that is consistent with the use of the prior art rapid release rivaroxaban tablets in a once daily dosage regimen for the treatment of thromboembolic disorders. For example, on information and belief,

the Kubitza Presentations disclose that the mean terminal half-life for rivaroxaban following the administration to healthy adults of prior art tablets containing 10 mg, 20mg, 40mg and 80 mg of rivaroxaban to healthy adults ranged from 7.60 to 17.40 hours, *see* Exhibit 2 at Table II and 419, and more specifically that the mean terminal half-life for the 10 mg rivaroxaban tablets was 9.07 hours, *id.* at Table II.

115. Additionally, on information and belief, the Kubitza Presentations disclosed that the inhibition of factor Xa activity by rivaroxaban following administration of the prior art rivaroxaban tablets at doses above 5 mg to healthy adults continued to be observed twenty-four hours after dosing. *Id.* at Figure 3A and 419.

116. On information and belief, the Kubitza Presentations also disclosed that the onset of factor Xa inhibition following administration of the prior art rivaroxaban tablets at doses above 5 mg to healthy adults occurred at the earliest time points tested, *i.e.*, in less than one hour. *Id.* at Figure 3A.

117. The Kubitza Presentations also were not disclosed in any IDS submitted during the prosecution of the ’218 patent. *See* Exhibit 1 07/27/2007 IDS submitted by Gray; 05/21/2008 IDS submitted by Hansen; 10/23/2008 IDS submitted by Hansen; 06/05/2009 IDS submitted by Hansen; 06/17/2011 IDS submitted by Hansen; 08/05/2016 IDS submitted by Hansen; and the two IDSs filed by Hansen on 11/21/2016.

118. Inventor Kubitza as an author of Kubitza et al.[1] and Kubitza et al.[2] and as the presenter of the Kubitza Presentations knew that the Kubitza Presentations disclosed additional information regarding the pharmacokinetic and pharmacodynamic properties of the prior art rivaroxaban tablets which was consistent with the use of the prior art rivaroxaban tablets in a once daily dosage regimen for the treatment of thromboembolic disorders that was not disclosed

in Kubitza et al.[1] and Kubitza et al.[2] and, therefore, knew that the disclosure of the Kubitza Presentations was not cumulative of Kubitza et al.[1] and Kubitza et al.[2] and was material to the prosecution and issuance of the ’218 patent. Inventor Kubitza, however, never disclosed this information to the PTO, despite acknowledging his clear duty pursuant to 37 C.F.R. § 1.56 to do so.

119. On information and belief, Gray, who was employed by Bayer Pharmaceuticals Corporation at the time of his involvement in the prosecution of the ’218 application, knew of the content of the Kubitza Presentations and that the disclosure of the Kubitza Presentation was material to the prosecution and issuance of the ’218 patent. Gray, however, never disclosed this information to the PTO, despite his clear duty pursuant to 37 C.F.R. § 1.56 to do so.

120. On information and belief, Hansen, who was retained on behalf of Bayer Pharmaceuticals Corporation and the Named Inventors during her involvement in the prosecution of the ’218 application, knew of the content of the Kubitza Presentations and that the disclosure of the Kubitza Presentation was material to the prosecution and issuance of the ’218 patent. Hansen however, never disclosed this information to the PTO, despite her clear duty pursuant to 37 C.F.R. § 1.56 to do so.

121. The Examiner issued a restriction requirement on November 10, 2010 requiring the patentees to elect a single invention from the following groups:

> Group I, claim(s) 7-8, drawn to a packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-chloro-N-([(58)-2-oxo-3-[4-(3-oxo-4-morphol inyl)phenyl]-1 ,3-oxazol id in-5-yl]methyl)-2-th iophenecarboxam ide and instructions for using said rapid-release tablet to treat a thromboembolic disorder.
>
> Group II, claim(s) 1-2 and 4-6 (in part), drawn to a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than one daily for at least five

> consecutive days in an oral dosage form to a patient in need thereof.
>
> Group Ill, claim(s) 3 and 4-6 (in part), drawn to a method of manufacturing a medicament using an oral dosage form of a direct factor Xa inhibitor. (It is noted that "use of" claims are rejected under 35 U.S.C. 101 and 35 U.S.C. 112, 2nd paragraph for being an improper method/process claim).

See Exhibit 1, 11/10/2010 Office Actin at 2.

122. The patentees elected Group II in part and amended the claims as follow:

> 1. (original) A method of treating a thomboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.
>
> 2. (original) The method of claim 1, wherein one dosage form is administered.
>
> 3, (original) The use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.
>
> 4. (currently amended) The method ~~or use as claimed in any of Claims 1 to 3~~ <u>of claim 1</u>, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.
>
> 5. (currently amended) The method ~~or as used in any of Claims 1 to 4~~ <u>of claim 1</u>**,** wherein the oral dosage form is a rapid-release tablet.
>
> 6. (currently amended) The method ~~or as used in any of Claims 1 to 5~~ <u>of claim 1</u>, wherein the direct factor Xa inhibitor is 5-Chloro-N-({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

7. (original) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1 ,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. (original) The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5 -Chloro-N -({ (5 S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1 ,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

9. (new) The method of claim 2, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

10. (new) The method of claim 2, wherein the oral dosage form is a rapid-release tablet.

11. (new) The method of claim 4, wherein the oral dosage form is a rapid-release tablet.

12. (new) The method of claim 2, wherein the direct factor Xa inhibitor is 5-Chloro-N({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1 ,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide.

13. (new) The method of claim 4, wherein the direct factor Xa inhibitor is 5-Chloro-N({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1 ,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide.

14. (new) The method of claim 5, wherein the direct factor Xa inhibitor is 5-Chloro-N({ (5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1 ,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide.

See Exhibit 1, 12/10/2010 Response to Election Requirement at 4 and 2-3.

123. The Examiner, in her March 17, 2011 Non-Final Office Action, rejected claims 1,

2, 4-6 and 9-14 for obviousness-type double patenting over claims 13, 24 and 30 of U.S. Patent No. 7,157,456 ("the '456 patent") and over claims 1-6 and 17-21 of U.S. Patent No. 7,592,3[9]9 ("the '399 patent") in view of Kubitza et al.[1] and Kubitza et al.[2]. *Id.* 03/17/2011 Office Action at 5-9.

124. The Examiner's pertinent reasoning for the obviousness-type double patenting rejections are set forth below:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).
>
> The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half life in a human patient. The patented claims do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.
>
> Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).
>
> Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release as claimed in the instant claims 5, 10, 11, and 14). Kubitza et al. also teach the plasma concentration half life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

> It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutives days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Id. at 6-9.

125. The Examiner also rejected the claims of the ’218 application under 35 U.S.C. § 103 over U.S. Patent Publication 2003/0156310 A1 (“Straub et al.”) in light of Kubitza et al.[1] and Kubitza et al.[2] as detailed below:

> 11. Claims 1-2, 4-6, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/0156310 A1) in view of Kubitza et al.[1] (“Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects,” *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Straub et al. do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. Straub et al. do not teach the plasma concentration half life in a human patient. Straub et al. do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release as claimed in the instant claims 5, 10, 11, and 14). Kubitza et al. also teach the plasma concentration half life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutives days as taught by Kubitza et al.[1] in order to

> effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Id. at 15-17.

126. A Response to Non-Final Office Action was filed by Hansen on June 17, 2011 which amended the claims of the '218 patent as follows:

1. (Currently amended) A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor **that <u>is 5-Chloro-N-({(SS)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide</u>** no more than once daily for at least five consecutive days in **[an] <u>a rapid-release</u>** oral dosage form **<u>or forms</u>** to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. (Cancelled).

3. (Cancelled).

4. (Previously presented) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. (Currently amended) The method of claim 1, wherein the oral dosage form **<u>or forms</u>** is a rapid-release tablet.

6. (Cancelled).

7. (Withdrawn) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(SS)-2-oxo-3-[4-(3-

oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet at a frequency of once daily.

8. (Withdrawn) A packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(SS)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

9. (Currently amended) The method of ~~claim 2~~ **claim 1**, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI)~~, Nan ST Segment Elevation 1\Lavenia Infarction (NSTEMI), unstable angina, reclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep - vein thromboses or stroke~~.

10. (Canceled).

11. (Currently amended) The method of claim 4, wherein the ~~oral dosage farm is a rapid release tablet~~ **thromboembolic disorder is Non ST Segment Elevation Myocardial Infarction (NSTEMI)**.

12-14. (Cancelled).

15. (New) The method of claim 1, wherein the thromboembolic disorder is unstable angina.

16. (New) The method of claim 1, wherein the thromboembolic disorder is reocclusion after angioplasty or aortocoronary bypass.

17. (New) The method of claim 1, wherein the thromboembolic disorder is pulmonary embolisms.

18. (New) The method of claim 1, wherein the thromboembolic disorder is deep vein thromboses.

19. (New) The method of claim 1, wherein the thromboembolic disorder is stroke.

Id. 06/17/2011 Response to Non-Final Office Action at 2-3.

127. Hansen made the following arguments in response to the Examiner's obviousness-type double patenting rejection in the June 17, 2011 Response.

Claims 1, 2, 4-6 and 9-14 stand rejected on the grounds of nonstatutory obviousness-type double patenting based on the same claims of the '456 and '339 patents discussed above, now in combination with Kubitza et al.[1] ("Multiple Dose Escalation Study Investigating the Pharmacodynamics, Safety and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects," Blood, vol. 102:11 (16 Nov. 2003), p. 811a) and Kubitza et al.[2] We respectfully disagree.

As discussed above, the patented claims do not disclose the presently claimed once daily dosage for at least five consecutive days of a rapid-release oral dosage form or forms. Kubitza et al.[1] and Kubitza et al.[2] do not provide the missing teaching. Kubitza et al.[1] and Kubitza et al.[2] report pharmacokinetic studies of rivaroxaban in ***healthy*** subjects. Neither reference discloses dosages required for efficacy in patients suffering from, or at risk from, a thromboembolic disorder. Furthermore, neither Kubitza et al.[1] nor Kubitza et al.[2] disclose that an efficacious dose would be a rapid-release dosage oral dosage form or forms administered once daily, as in the presently claimed methods.

The Office Action alleges that one of ordinary skill in the art would have been motivated to administer rivaroxaban for five consecutive days as taught by Kubitza et al.[1] to effectively treat deep vein thromboses. The Office Action also alleges that one of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet of Kubitza et al.[2] to provide patient convenience and compliance.

However, to the contrary, the person of ordinary skill in the art looking for an effective dose of rivaroxaban would have looked at half life and pharmacokinetics of rivaroxaban. These considerations lead away from once daily dosing with a rapid-release oral dosage form. As discussed above, it was well known to a person of ordinary skill in the art that a drug having a half life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid-release form. Accordingly, one of ordinary skill in the art would not have been motivated to administer rivaroxaban only once daily and in a rapid-release dosage form because successful therapy was not expected.

> It had been demonstrated by preclinical investigations that the k_i value for free factor Xa is 0.4 nM, which would be equivalent to a plasma concentration of approximately 0.17 microgram/L of unbound rivaroxaban. The administration of 10 mg rivaroxaban once daily in phase II studies resulted in free plasma concentrations at trough of 0.91 microgram/L, which is approximately five-fold higher than the k_i value for free factor Xa. Therefore, the offset of action can be described by the elimination of rivaroxaban from plasma, which, based on an elimination half life of 11-13 hours, can be assumed to be between 48-72 hours after the last intake of rivaroxaban 10 mg rapid release tablet. This supports the once-daily dosing regimen for rivaroxaban.
>
> The Office Action alleges that a person of ordinary skill in the art would have had a reasonable expectation of success with once daily rivaroxaban administration for five consecutive days because rivaroxaban was known to treat venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] disclose safe and tolerable rivaroxaban dosages. However, as discussed above, the person of ordinary skill would have looked at the half life of rivaroxaban and expected that if a rapid-release oral dosage form was administered, it must be administered more frequently than once daily. Accordingly, for the reasons stated above, the cited references would not have provided one of ordinary skill in the art with a reasonable expectation of successful therapy with the recited dosage form and regimen.

Id. at 5-7.

128. Hansen made the following arguments in response to the Examiner's rejection under 35 U.S.C. § 103 in the June 17, 2011 Response.

> As the Office Action admits, Straub et al. does not teach administering rivaroxaban once daily for at least five consecutive days, or the plasma concentration half life of rivaroxaban. The Patent Office has also not found a teaching in Straub et al. of a rapid-release tablet.
>
> The Office Action relies on Kubitza et al.[1] and Kubitza et al.[2] for teaching administering 5 mg of rivaroxaban once daily for 4-8 days, dosing rivaroxaban to men with rapid onset of action, a 2-hour half life of a rivaroxaban tablet, and safe and well-tolerated dosages across a range of oral dosages of 1.25 mg to 80 mg. Yet as discussed above in the discussion of the double patenting rejection, Kubitza et al.[1] and Kubitza et al.[2] disclose administration to healthy subjects, and do not disclose that once daily oral dosaging of a rapid-release form of rivaroxaban for at least five days would be efficacious.

Furthermore, for the same reasons discussed above, the person of ordinary skill in the art would not have been motivated to modify the dosages taught for once daily administration of a rapid-release form, nor would the person have expected such a treatment regimen to be successful because of the half life of rivaroxaban. Contrary to the conclusions in the Office

Action, a reasonable expectation of success with the claimed dosing regimen cannot be found in the Kubitza et al.[1] and Kubitza et al.[2] disclosures of safe and tolerable dosages when the art accepted the primacy of pharmacokinetic values such as half life in determining a likely successful oral dosage regimen.

[1] Straub et al. is the published application that resulted in the granted '456 patent discussed in the double patenting rejections above. Also, for clarity, the Office Action transposes two numbers in the Straub et al. publication number, US 2003/015**63**10, but the correction is obvious so we address the application 2003/015**36**10.

8

Id. at 8-9.

129. On information and belief, Hansen's argument that "neither Kubitza et al.[1] nor Kubitza et al.[2] disclose that an efficacious dose would be a rapid-release [ ] dosage form or forms administered once daily, as in the presently claimed methods" is directly contradicted by the Kubitza Presentations' disclosure that factor Xa inhibition was observed less than one hour following administration of the prior art rivaroxaban tablets. As such, the knowing failure of Inventor Kubitza, Gray and/or Hansen to disclose the Kubitza Presentations to the PTO was an omission that was material to the prosecution and issuance of the '218 patent and this material omission was made with the intent to deceive the PTO.

130. The Examiner issued a Final Office Action on September 21, 2011 which included the following response to the arguments made in the June 17, 2011 Response to Non-Final Office Action.

> Applicants argue that one of ordinary skill in the art looking for an effective dose of rivaroxaban would have looked at half-life and pharmacokinetics of rivaroxaban leading away from once daily dosing with a rapid-release oral dosage form. Applicants argue that it was well known to a person of ordinary skill in the art that a drug having a half-life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid-release form. In response it is respectfully submitted that Kubitza et al.[1] and Kubitza et al.[2] both teach once daily dosing of a rapidly releasing tablet. Further, a once daily dosage at a higher dosage is sometimes preferred in instances where patient compliance is an issue.

Id. 09/21/2011 Final Office Action at 4-7.

131. In light of the above, the Examiner maintained the obviousness-type double patenting rejection of claims 1, 4, 5, 11 and 18 of the ’218 patent over the ’456 patent in view of Kubitza et al.[1] and Kubitza et al.[2]. *Id.* at 9-11.

132. Additionally, the Examiner maintained the obviousness-type double patenting rejection of claims 1, 4, 11 and 18 over the ’339 patent in view of Kubitza et al.[1] and Kubitza et al.[2]. *Id.* at 11-13.

133. The Examiner also maintained the rejection of claims 1, 4, 5, 11 and 18 under 35 U.S.C. § 103 over Straub et al. in view of Kubitza et al.[1] and Kubitza et al.[2]. *Id.* at 14-17.

134. A Response to Final Office Action was filed by Hansen on January 30, 2012, which amended the claims of the ’218 application as follows:

> 1. (Currently amended) A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl }methyl)-2-thiophenecarboxamide no more than once daily for at least five consecutive days in a rapid-release oral dosage form **~~or forms~~** to a patient in need thereof**~~, wherein said inhibitor has a~~**

~~**plasma concentration half life of 10 hours or less when orally administered to a human patient**~~

2. (Canceled).

3. (Canceled).

4. (Previously presented) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. (Currently amended) The method of claim 1, wherein the oral dosage form ~~**or forms**~~ is a rapid-release tablet.

6. (Canceled).

7. (Withdrawn) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(SS)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet at a frequency of once daily.

8. (Withdrawn) A packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(SS)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

9. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI).

10. (Canceled).

11. (Previously presented) The method of claim 4, wherein the thromboembolic disorder is Non ST Segment Elevation Myocardial Infarction (NSTEMI).

12-14. (Cancelled).

15. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is unstable angina.

16. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is reocclusion after angioplasty or aortocoronary bypass.

17. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is pulmonary embolisms.

18. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is deep vein thromboses.

19. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is stroke.

Id. 01/30/2012 Response to Final Office Action at 2-3 and 11.

135. The arguments presented by Hansen as to the obviousness and obviousness-type double patenting rejection contain the following description of the content of Kubitza et al.[1] and Kubitza et al.[2]:

> Furthermore, both abstracts report a half life for rivaroxaban that would lead the ordinary artisan to expect that multiple daily dosages would be required. When a drug substance is applied in no more than a therapeutically effective amount, which is usually preferred to minimize the exposure of patients and avoid side effects, the drug must be given approximately every half life. See specification at page 3 lines 4-8, citing Malcolm Rowland and Thomas Tozer, "Clinical Pharmacokinetics," 1995, pp.83. Both Kubitza[1] and Kubitza[2] report half lives for rivaroxaban that would indicate multiple daily dosages were required: a half life of 4-6 hours (Kubitza[2]) or 3-4 hours (Kubitza[1]).

Id. 01/30/2012 Response to Final Office Action at 8.

136. On information and belief, Hansen's argument that "both Kubitza et al.[1] nor Kubitza et al.[2] report half-lives for rivaroxaban that would indicate multiple daily dosages were required: a half-life of 4-6 hours" is directly contradicted by the Kubitza Presentations' disclosure that the prior art rivaroxaban 10mg, 20 mg, 40 mg and 80 mg tablets had mean

terminal half-lives ranging from 7.60 to 17.40 hours and more specifically that the 10 mg prior art rivaroxaban tablet had a mean half-life of 9.07 hours. As such, the knowing failure of Inventor Kubitza, Gray and/or Hansen to disclose the Kubitza Presentations to the PTO was an omission that was material to the prosecution and issuance of the '218 patent and this material omission was made with the intent to deceive the PTO.

137. A Notice of Appeal and an Appeal Brief were submitted by Hansen on February 21, 2012 and April 20, 2012, respectively. *Id.* 02/21/2101 Notice of Appeal and 04/20/2012 Appeal Brief at 11.

138. The Appeal Brief contains the following pertinent characterization of Kubitza et al.[1] and Kubitza et al.[2]:

> Additionally, both Kubitza abstracts report a half-life for rivaroxaban that would lead the ordinary artisan to expect that multiple daily dosages would be required. Specifically, when a "drug substance is applied in no more than a therapeutically effective amount, which is usually preferred in order to minimize the exposure of patients with that drug substance in order to avoid side effects, the drug must be given approximately every half-life." (Specification at page 3, lines 4-8, citing Malcolm Rowland and Thomas Tozer, "Clinical Pharmacokinetics," 1995, p. 83). It is well known to a person of ordinary skill in the art that a drug having a half-life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid release form. (See, *e.g.*, Specification at page 3, lines 15-18). Both Kubitza[1] and Kubitza[2] report half-lives for rivaroxaban that would indicate multiple daily dosages were required: Kubitza[2] reports a half-life of 4-6 hours while Kubitza[1] reports a half-life of 3-4 hours. Therefore, one of skill in the art would not have been motivated to administer rivaroxaban only once daily and in a rapid-release dosage form because successful therapy would not have been expected.

Id. 04/20/2012 Appeal Brief at 8.

139. The Board of Patent Appeals in their June 3, 2016 Decision made the following findings as to the disclosures of Kubitza et al.[1] and Kubitza et al.[2]:

> The Examiner conceded that the Straub 456, Straub 339, and Straub 610 references did not claim or disclose the "rapid release" tablet of claim 5. Final Action 10, 12, 15–16. For this, the Examiner relied on Kubitza 2, which disclosed "BAY 59-7939 showed a rapid onset of action with maximal effects being observed after 2 hours" and "peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Kubitza 2 (Abstract); *see also* FF11; Final Action 16 and Ans. 13 (discussing Kubitza 2).
>
> Appealed claim 5 recites a "*rapid-release tablet*," which we interpret in view of the express definition thereof provided in the Specification, which is "those [tablets] which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %." FF4. The only disclosure of Kubitza 2 directed to drug release by tablets is that "[l]ower peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Kubitza 2 (Abstract). Based on the evidence of record we cannot conclude that this disclosure indicates a "rapid-release tablet" as defined in the Specification. Moreover, the Examiner has offered no explanation as to how the disclosure of Kubitza 2 teaches or suggest a rapid-release tablet in line with the interpretation of this claim language. Therefore, we find Appellants' argument (*see* App. Br. 9) concerning the patentability of claim 5 over the combined references persuasive and reverse the Examiner's rejections of claim 5 over Straub 456, Straub 339, or Straub 610 in view of or combined with Kubitza 1 and Kubitza 2.

Id. 06/03/2016 Board of Patent Appeals Decision at 8-9.

140. The decision of the Board of Patent Appeals, which was based on their finding that Kubitza et al.[2] disclosed that "lower peak concentrations of approximately 50% were observed 2 hours after administration of the [rivaroxaban] tablet" was insufficient to conclude that Kubitza et al.[2] disclosed a rapid-release tablet, *id.,* is directly contradicted by the Kubitza Presentations' disclosure that factor Xa inhibition was observed less than one hour following administration of the prior art rivaroxaban tablets. As such, the knowing failure of Inventor

Kubitza, Gray and/or Hansen to disclose the Kubitza Presentations to the PTO was an omission that was material to the prosecution and issuance of the ’218 patent and this material omission was made with the intent to deceive the PTO.

141. The Examiner, in her August 29, 2016 Notice of Allowability withdrew the obviousness-type double patenting rejection over the ’456 patent in light of Kubitza et al.[1] and Kubitza et al.[2] in light of the decision of the Board of Patent Appeals. *Id.* 08/29/2016 Notice of Allowability at 3.

142. The Examiner, in her August 29, 2016 Notice of Allowability withdrew the obviousness-type double patenting rejection over the ’399 patent in light of Kubitza et al.[1] and Kubitza et al.[2] in light of the decision of the Board of Patent Appeals. *Id.* at 4.

143. Based on the material omissions by Inventor Kubitza, Gray and/or Hansen detailed above, which were made with the intent to deceive the Examiner and Board of Patent Appeals, the ’218 patent is unenforceable due to inequitable conduct.

144. InvaGen is entitled to a declaration that the claims of the ’218 patent are unenforceable due to inequitable conduct.

PRAYER FOR RELIEF

WHEREFORE, InvaGen Pharmaceuticals, Inc. respectfully prays for judgment in its favor and against Plaintiffs/Counterclaim Defendants as follows:

1. Declaring that the manufacture, use, sale, offer for sale, or importation of the drug product that is the subject of ANDA No. 208543 has not infringed, does not infringe and would not infringe any valid or enforceable claim of the ‘218 patent.

2. Declaring that the claims of the ‘218 patent are invalid.

3. Declaring that the claims of the ’218 patent are unenforceable due to inequitable conduct.

4. Ordering that Plaintiffs/Counterclaim Defendants’ Complaint be dismissed in its entirety with prejudice and judgment in favor of InvaGen Pharmaceuticals, Inc.

5. Declaring this case exceptional and awarding InvaGen Pharmaceuticals, Inc. its costs and disbursements, including its attorneys’ fees pursuant to 35 U.S.C. § 285 and/or this Court’s inherent authority.

6. Ordering that the effective date of the approval of InvaGen Pharmaceuticals, Inc.’s ANDA is immediate under §505(j) of the Federal Food Drug and Cosmetic Act, 21 U.S.C. §355(j), upon a statement by the FDA that it is otherwise ready to approve the ANDA.

7. Awarding Defendant such other and further relief as the Court may deem just and proper.

Respectfully submitted,

/s/ R Touhey Myer
R Touhey Myer (#5939)
CAESAR RIVISE, PC
800 N. King Street - Suite 304
Wilmington, DE 19801
(302) 544-9100
tmyer@crbcp.com

Attorneys for Defendant
InvaGen Pharmaceuticals, Inc.

OF COUNSEL:

Robert S. Silver *(Pro Hac Vice Anticipated)*
Lynn Terrebonne *(Pro Hac Vice Anticipated)*
CAESAR RIVISE, PC
1635 Market Street
Seven Penn Center – 12th Floor
Philadelphia, PA 19103
(215) 567-2010

Dated: August 1, 2017